REMARKS

Reconsideration and withdrawal of the rejections of the application are requested in view of the amendments and remarks herewith, which place the application into condition for allowance. The Examiner is thanked for courtesies extended during the December 3, 2003 telephonic interview.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 47, 49-51, 53-55, 57 and 59-83 are pending in this application. Claims 1, 6, 47, 50, 51, 55, 57, 60-62, and 74-78 are currently amended; claims 80-83 have been added to round out the scope of protection to which Applicants are entitled.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims are and were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Support for Amended and Newly Added Claims

Claims 1 and 57: Support for "spliced out of RNA transcribed from the retroviral vector" is shown pictorially in the "Vector" panels of Figure 27c. (Figure 27c covers two pages; the first page is referred to as "Figure 27c" and the second page is referred to as "Fig 27c cont". It is the first page of 27c to which we refer throughout this Response for more particular support for the claimed invention.) See also page 9 of this Response, which includes a more simplistic pictorial of this concept in parts B1 and B2.

Claims 47 and 74: Support for introducing a pro-vector into a packaging cell can be found throughout the specification, and in particular, in the section beginning on page 11, line 19. Support for the vector comprising a packaging signal was formerly found in dependent claim 51, and can also be found, *inter alia*, on page 33, lines 23-24, of the specification and in Figure 27c. In Figure 27c, the packaging signal is designated as ψ.

Claims 55 and 75: Support for a non-retroviral transcriptional control sequence can be found in the paragraph beginning on page 83, line 27, wherein a heterologous (*i.e.* non-retroviral)

promoter is discussed in relation to the expression of lentiviral components. Page 43, lines 15-30, and page 41, lines 14-30, provide further explanation of what is meant by "non-retroviral" transcriptional control sequences. To this end, Figures 18 and 21-23 show the use of the CMV promoter in the context of retroviral expression components; and, Figure 17 shows the use of a hypoxia response element as a promoter in the context of retroviral expression components.

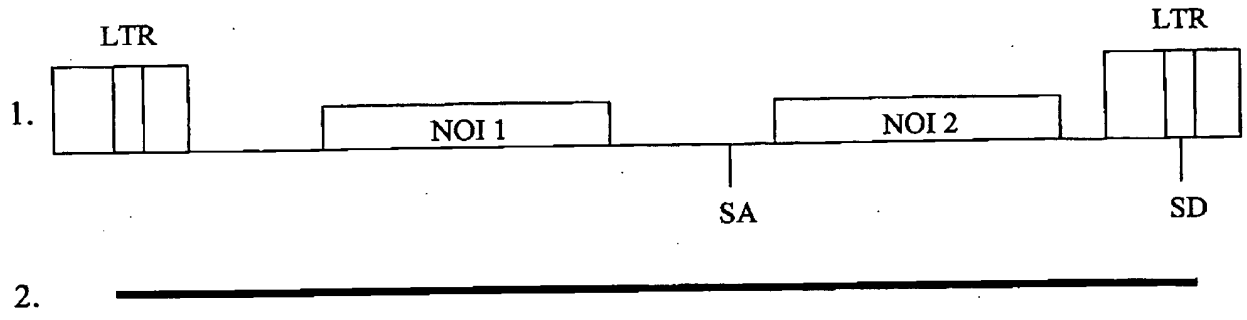
Support for the retroviral pro-vector of claim 80 can be found in the first diagram of Figure 27c, under "Pro-vector"; and support for the retroviral pro-vector of claim 82 can be found in the first diagram of Figure 18, where 3'-p450 is the NOI. Support for a retroviral particle comprising a pro-vector, as claimed in claims 81 and 83, can be found throughout the specification, and in particular, in the paragraph beginning on page 2, line 6. Support for "retroviral vector particle" may also be found at page 39, lines 13-16.

The remaining claim amendments place the claims in better form and do not affect their scope. No new matter is added.

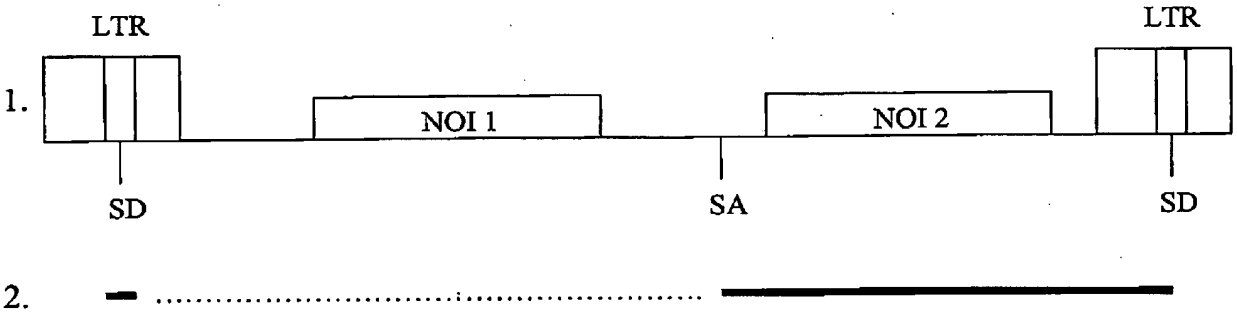
Summary of the Invention

The present invention involves a system for delivering a nucleotide of interest (NOI) to a target cell, using a retroviral vector containing splice donor and splice acceptor sites. The invention is best understood by means of the following schematic diagram, which is a simplified reproduction of Figure 27c, wherein LTR = long terminal repeats, NOI = nucleotide of interest, SA = splice acceptor and SD = splice donor.

A. Pro-vector



B. Vector



Part A1 shows the configuration of the pro-vector DNA, which is transcribed, for example in a producer or packaging cell, to yield the corresponding pro-vector RNA, shown in part A2. Claim 80 claims this pro-vector; and, claim 82 claims an analogous pro-vector, wherein NOI1 is not required.

The pro-vector of A2 can subsequently be packaged into a retroviral particle, as claimed in claims 81 and 83, and introduced into a target cell. In the target cell, the RNA pro-vector is reverse transcribed to yield the DNA vector configuration shown in B1. It is this configuration that is claimed in claim 1, and also in claim 57, where NOI1 is referred to as "an intervening sequence".

As is explained beginning on page 5 of the specification, reverse transcription results in a duplication of the LTRs, such that a copy of the SD from the 3' LTR of the pro-vector is made in

the 5' LTR of the vector. Note that this consequence of reverse transcription is simply a duplication, not a translocation, and thus, an irrelevant copy of the SD also remains in the 3' LTR.

The vector of B1 becomes integrated into the chromosomal DNA of the target cell, where it can be transcribed by the cell's transcriptional machinery into RNA, which is then spliced to result in the molecule depicted in B2 of the above diagram. As this is simply an RNA encoding a molecule of interest, it is not claimed. In the schematic above, and in the vector of claim 1, the first NOI would be spliced out, while in claim 57, the sequence to be spliced out is called "an intervening sequence". These sequences have not yet been spliced out of the claimed vectors, however, which are in the form shown in B1.

Claim 47 is a method of producing the retroviral vector of claim 1 by the process described in the above discussion. Similarly, claim 74 is a method of producing the retroviral vector of claim 57. The remaining claims are dependent claims, which further specify certain aspects of the invention.

II. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH, ARE OVERCOME

The Application Contains Adequate Written Description

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-79 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description because the Office Action argues that the recitations "whereby the first NOI is removed as a result of splicing" in claim 1, and "whereby an intervening sequence between the functional splice donor site and the functional splice acceptor site is removed as a result of splicing" in claim 57, are new matter. The rejection is traversed.

As is explained above and shown in Figure 27c of the application, NOI1, or the first NOI, is spliced out of the RNA transcribed from the claimed vector. This spliced version is not claimed, and the recitation was not meant to imply that the first NOI is not present in the claimed vector (it is present as element (d) of claim 1). Rather, this recitation was added so that functional language was present in the claim to exclude the presence of a cryptic splice site that would result in incorrect or incomplete splicing. The phrasing of this aspect has been amended to clarify this intention.

As was stated in the last paragraph on page 12 of the Amendment filed on July 14, 2003, support for removal of an intervening sequence between the SD and SA by splicing is shown in

the diagram on page 31 of the application. Page 8 of the Amendment erroneously referred to page 30, lines 31-32, of the specification, and Applicants regret any confusion caused by this typographical error.

It is therefore submitted that no new matter has been added, and that the claims comply with the written description requirement set forth in the first paragraph of 35 U.S.C. §112.

The Claims Are Enabled

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-79 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejection is traversed, and the Examiner is requested to clarify his position with respect to enablement. For example, page 3 of the Office Action states that this rejection is maintained for reasons of record. The reasons of record related to the potential presence of cryptic splice sites, which, as explained on pages 14-15 of the Amendment filed on July 14, 2003, can routinely be identified and removed by one of skill in the art. These arguments were not addressed by the Examiner, nor does the discussion in the Office Action relate to that issue. The Examiner is thanked for indicating during the December 3, 2003 telephonic interview that the arguments previously presented by the Applicants with respect to cryptic splice sites were persuasive, and it is requested that this view be confirmed for the record.

With respect to the Examiner's view of the invention, presented on pages 4-7 of the Office Action, Applicants take this opportunity to clarify the Examiner's understanding. For example, the first paragraph on page 4 of the Office Action contains some inaccuracies, which may have been resolved by the above discussion. Page 4 states: "The virus integrated into the genome of the target cell is spliced and is shown in Fig. 27c. The virus integrated into the genome of the target cell has a 3' LTR with a splice donor, a portion of the 5' LTR and the second NOI. The virus integrated into the genome of the target cell does not have the entire 5' LTR or the first NOI (selectable marker/packaging signal) as claimed (1, 57). The virus integrated into the genome of the target cell has a splice donor fused with a splice acceptor and not a splice donor and acceptor as claimed (1, 57)."

Referring to the diagram on page 9, above, it is the vector of part B1 that is integrated into the genome of the target cell, and that is claimed in claims 1 and 57. When it is integrated into the genome of the target cell, it is in the form of DNA, and is not spliced. Upon transcription of B1 into a corresponding RNA (not shown), the corresponding RNA is spliced, as shown in B2.

Therefore, the virus that gets integrated into the genome, and the claimed vector, has the entire 5' LTR, the first NOI or intervening sequence, a splice donor and a splice acceptor, as specified in claims 1 and 57.

The Office Action goes on to state, on page 4, that "the viruses of claims 1 and 57 are never in a retroviral particle as in claims 24 and 58". This is true, and the Examiner is thanked for raising the point. It is the pro-vector, as claimed in claims 80 and 82, that is incorporated into a viral particle. Claims 24 and 58 have been cancelled, and claims 81 and 83, depending on claims 80 and 82, respectively, have been added to correct this issue.

Contrary to statements on pages 5 and 6 of the Office Action, a selectable marker is not an essential component of the claimed vectors or pro-vectors. While the first NOI can be a selectable marker in one embodiment, it is not required in every embodiment. For example, routine techniques for simple and reliable selection of retroviral producer clones, without the need for selectable markers, were available prior to the time the claimed invention was made. Single cell cloning, following electroporation, lipofection, or calcium phosphate techniques, is often used for screening for a virus. In addition, Onodera *et al.* (*Human Gene Therapy* 8:1189-1194; July, 1997; abstract enclosed) teaches a technique, called RNA dot blot, that was designed to screen for retroviral producer clones without the need for selectable markers.

Pages 5 and 6 of the Office Action also state that the packaging signal is essential to package the pro-virus into viral particles. This is true, and the recitation of a packaging signal has been added to the vector in the method claims (47 and 74). However, the ability to be packaged is not essential to the vector claims, and a packaging signal is not recited in these claims. For instance, the vector of claim 1 could be introduced into a cell by a method other than viral infection. As long as reverse transcriptase were also provided to the cell, the claimed vector could still function as intended without having been packaged in a viral particle.

Pages 5 and 6 also contain misstatements with respect to the presence and location of the first NOI, the splice donor site and the splice acceptor site in the claimed vectors. It is assumed that the explanations provided herein have clarified these aspects of the invention. If this is not the case, the Examiner is welcome to contact the undersigned for further clarification.

On page 6 of the Office Action, it is argued that the phrase "packaging the retroviral pro-vector in a packaging cell, thereby producing a viral particle", in claims 47 and 74, lacks essential elements. This language has been removed and new language has been added to claims 47 and 74

to address this point. The Office action also states that the phrase "infecting a target cell ... thereby producing a retroviral vector comprising a functional splice donor site with its 3' [sic] LTR" lacks essential elements, and then goes on to state that "the specification does not teach that reverse transcription as claimed ensures translocation of the splice donor". Firstly, reverse transcription is not claimed; however, it is recited, as it does occur in the target cell. Secondly, the specification does teach that reverse transcription results in translocation of the splice donor. The paragraph bridging pages 5 and 6 of the application teaches that the 5' and 3' sequences are duplicated as a result of two jumps of the reverse transcriptase. Therefore, a splice donor sequence, or any other sequence placed in the repeat regions at either end of the pro-vector, will be duplicated to the other end, upon reverse transcription.

It is believed that the claims are enabled by the specification. Reconsideration and withdrawal of all the 35 U.S.C. §112, first paragraph, rejections are requested.

III. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH ARE OVERCOME

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-79 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The rejections are traversed.

Claims 1 and 57 were deemed indefinite due to a misunderstanding of what is claimed. It is assumed that the foregoing discussions have cleared up any confusion with respect to the elements present in the claimed vectors. If this is not the case, the Examiner is welcome to contact the undersigned for further discussion and/or clarification.

Claim 6 has been amended to correct the antecedent basis.

As discussed above, claims 47 and 74 have been amended to clarify that the pro-vector contains a packaging signal, and is therefore packaged into a viral particle in the packaging cell. Further, as is also discussed above, reverse transcription does ensure duplication of the splice donor site to the 5' LTR. The mechanism of action of reverse transcriptase is taught in the specification, beginning on page 5.

The word "heterologous" has been removed from the claims, and the word "non-retroviral" has been substituted therefor in independent claims 55 and 75.

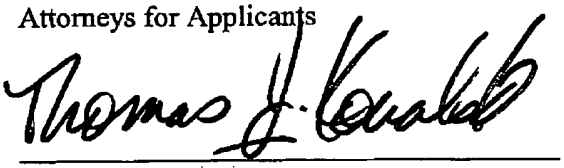
Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are requested.

CONCLUSION

As it is believed that this application is in condition for allowance an early notice to that effect is earnestly solicited. If, however, there remains any issue outstanding, the Examiner is invited to contact the undersigned for its prompt attention.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Applicants

By: 

Thomas J. Kowalski
Reg. No. 32,147

Anne-Marie C. Yvon, Ph.D.
Reg. No. 52,390
(212) 588-0800